



Role of Liver in Heme Synthesis

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INTENDED LEARNING OBJECTIVES (ILOs)



By the end of this lecture the student will be able to:

- 1. Outline the structure of porphyrins**
- 2. Illustrate the steps of heme synthesis**
- 3. Discuss regulatory steps of heme synthesis**



Outlines

What is Heme?

Steps of heme synthesis

Regulation of heme synthesis

What is Heme?

?What is Heme

Heme is the *colored prosthetic group* of **hemoglobin** and a number of proteins called **hemoproteins**



Some important heme- proteins

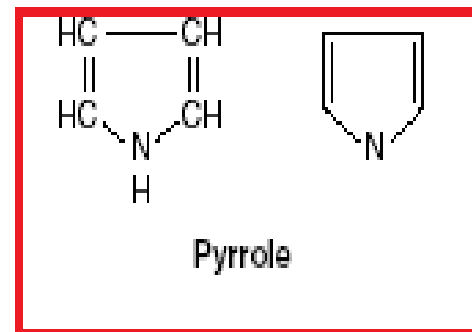
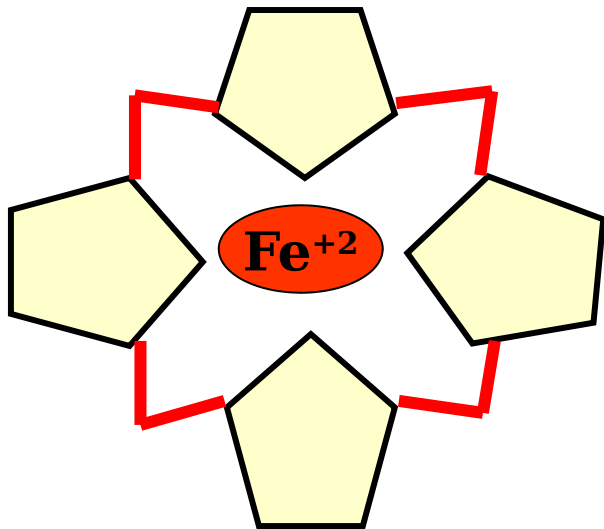
- **Electron transport chain cytochromes (cyt aa3, cyt.c)**
- **Cytochrome P450**
- **Catalase and Peroxidase (degradation of H₂O₂)**
- **Tryptophan pyrrolase**
- **Cytoplasmic guanylate cyclase (activated by NO)**



Structure Of Heme

+ porphyrin

Porphyrins = cyclic compounds formed of four pyrrole rings



Heme group

Porphyrins

They are **cyclic** compounds

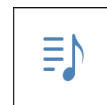
formed of

4 pyrrole rings linked by **methenyl**

bridges.
They form **complexes** with **metal**
ions that bind to **Nitrogen** of
:pyrrole rings

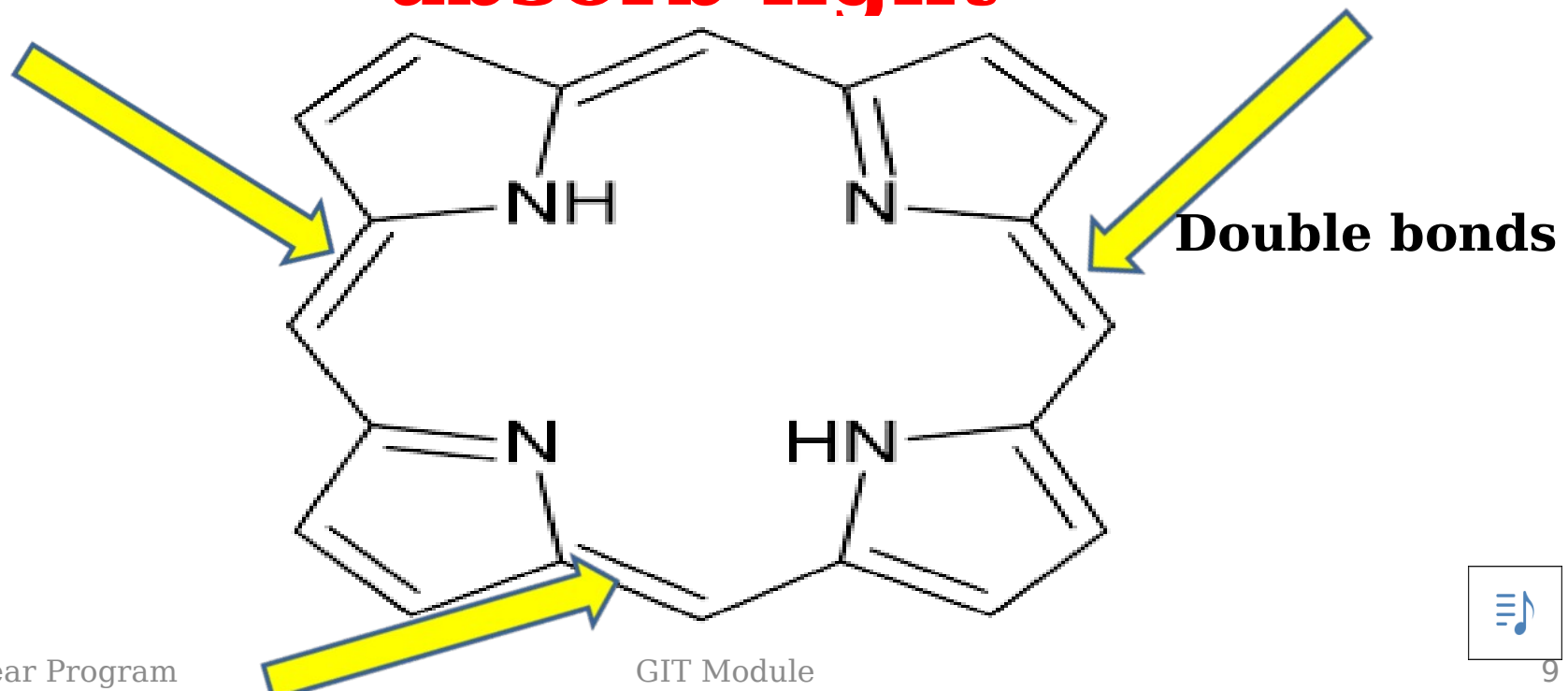
,Iron porphyrins (Heme)

Magnesium porphyrins



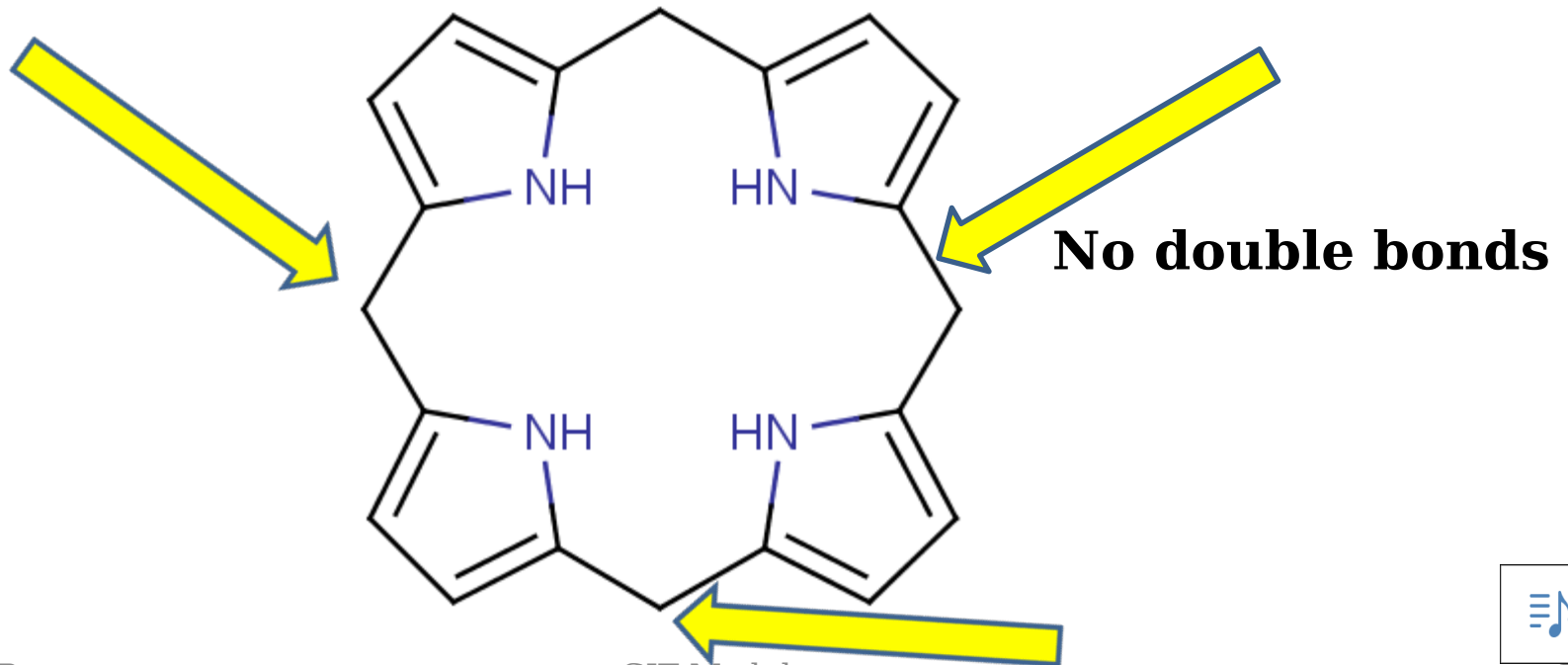
Structure Of Porphyrins

conjugated **double bonds** which
absorb light



Porphyrinogens

They are **reduced** forms of porphyrins that have **no** conjugated **double bonds** and



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**Porphyrin ring present in all of -1
:the following except**

- A. peroxidase**
- ☒ B. Xanthine oxidase**
- C. Tryptophan pyrrolase**
- D. catalase**
- E. guanylyl cyclase**



Steps of heme synthesis

Mainly in the **bone marrow** (hemoglobin synthesis) and the **liver** (cytochrome P450 synthesis)

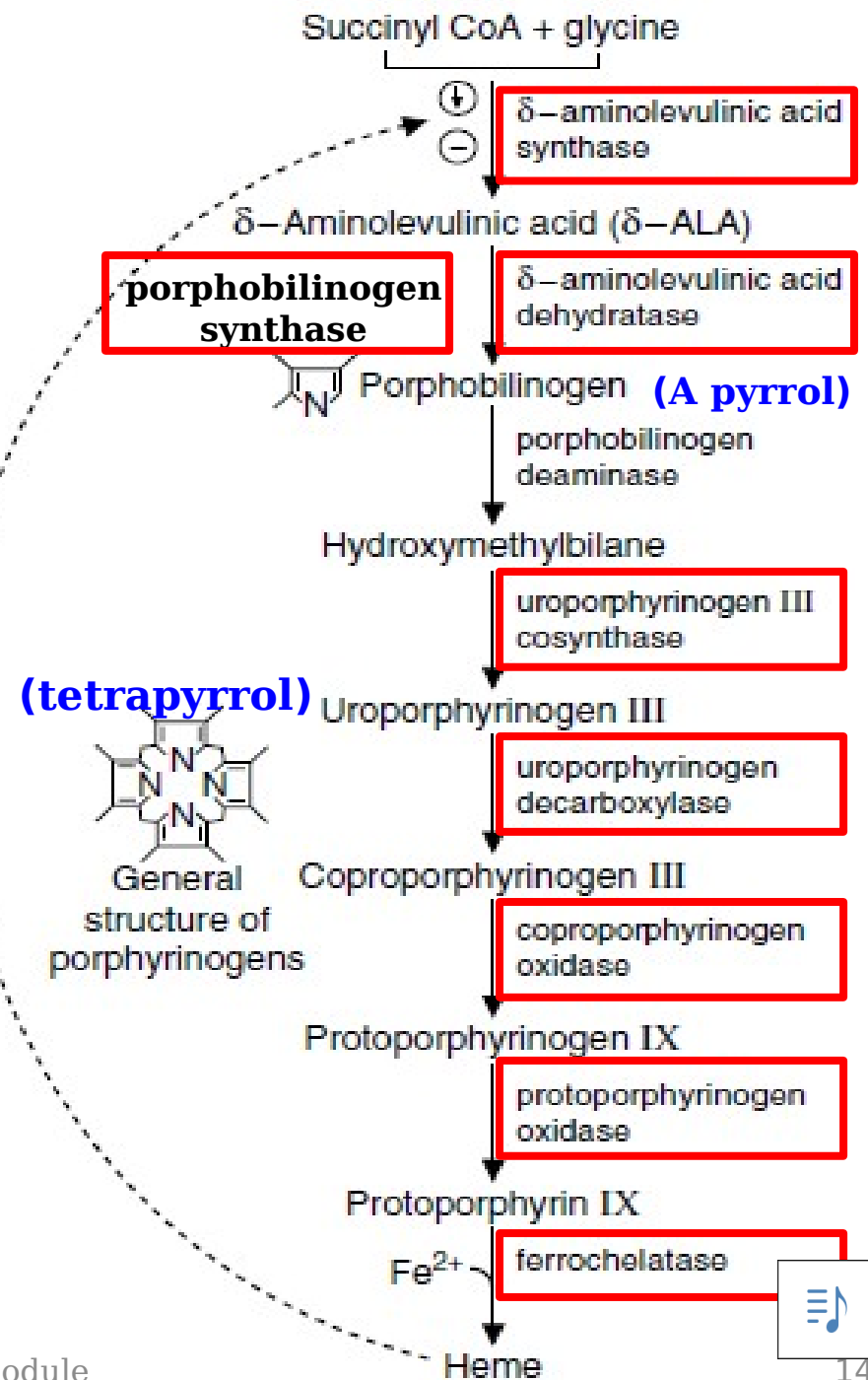
Heme biosynthetic pathway is partly **mitochondrial** and partly **cytosolic**

The reactions are **Irreversible**

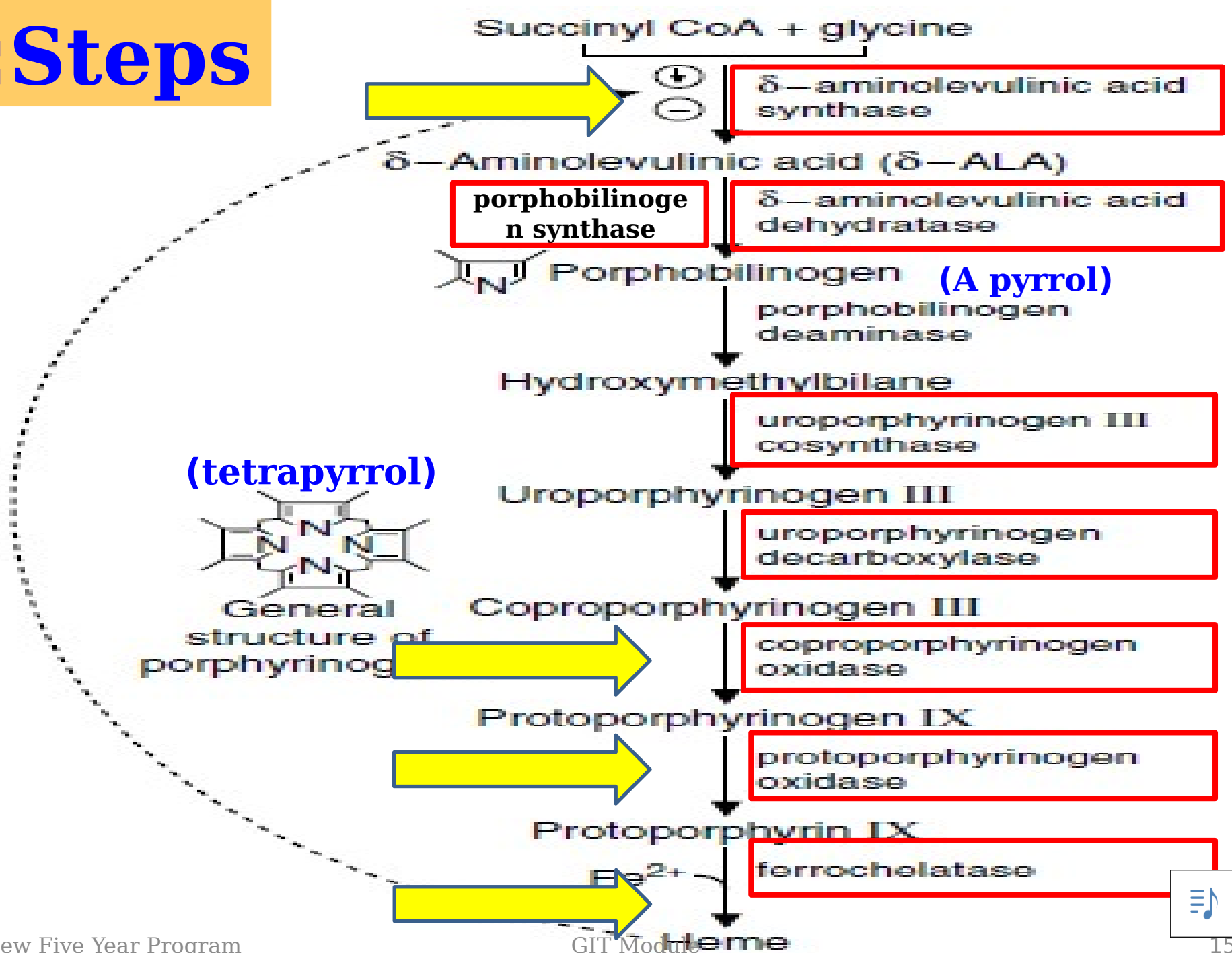


:Steps

The **initial** reaction and the **last three** steps in the formation of porphyrins occur in **mitochondria**, but the **intermediate** steps occur in the **cytosol**.



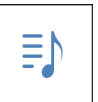
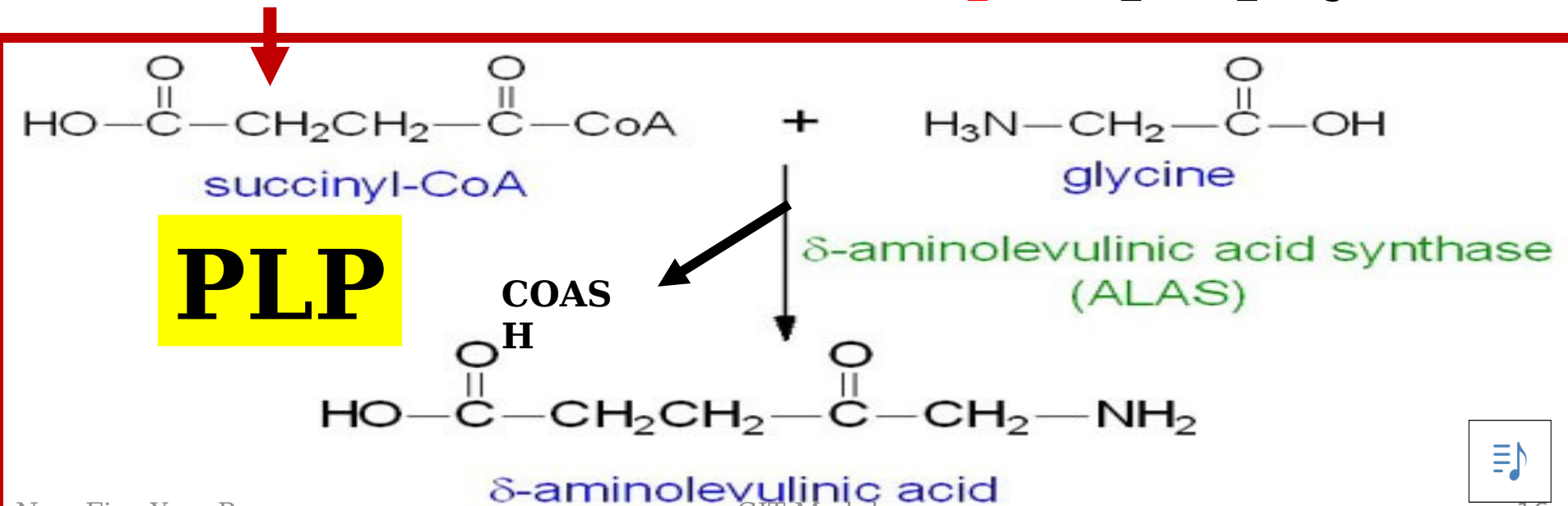
:Steps



Formation of δ -aminolevulinic acid -1 : (ALA)

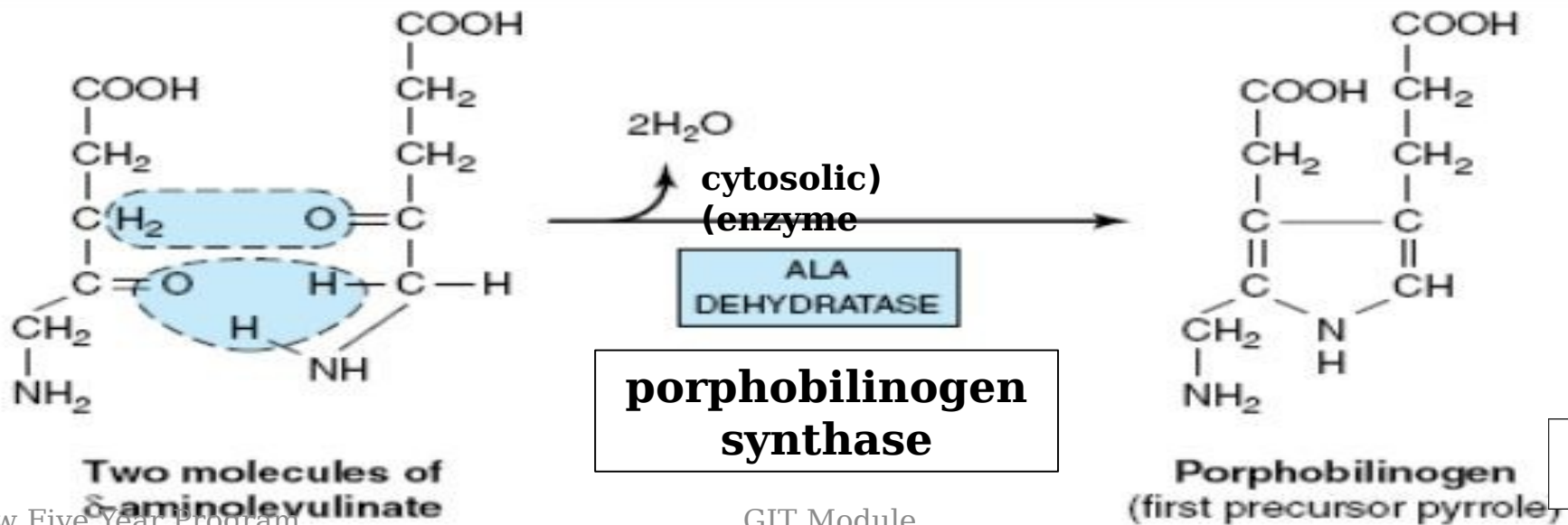
- **Glycine** and **succinyl CoA** condense to form **ALA** by mitochondrial **ALA synthase** (ALAS).

• It is the **committed step** in porphyrin



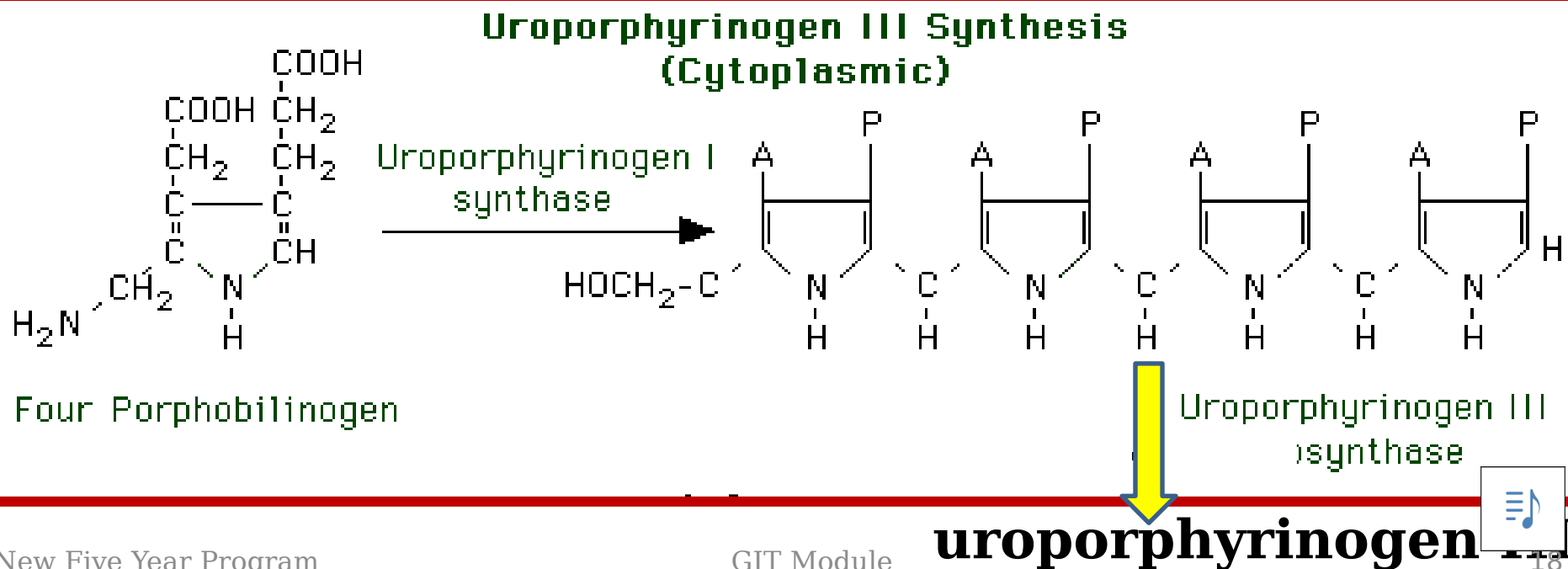
2-Formation of porphobilinogen:

- Condensation of **two** molecules of **ALA** by **Zn-containing cytosolic ALA dehydratase** (porphobilinogen synthase).
- It is **inhibited** by **heavy metal ions** e.g. **lead** that replace the zinc .



3- Formation of uroporphyrinogen:

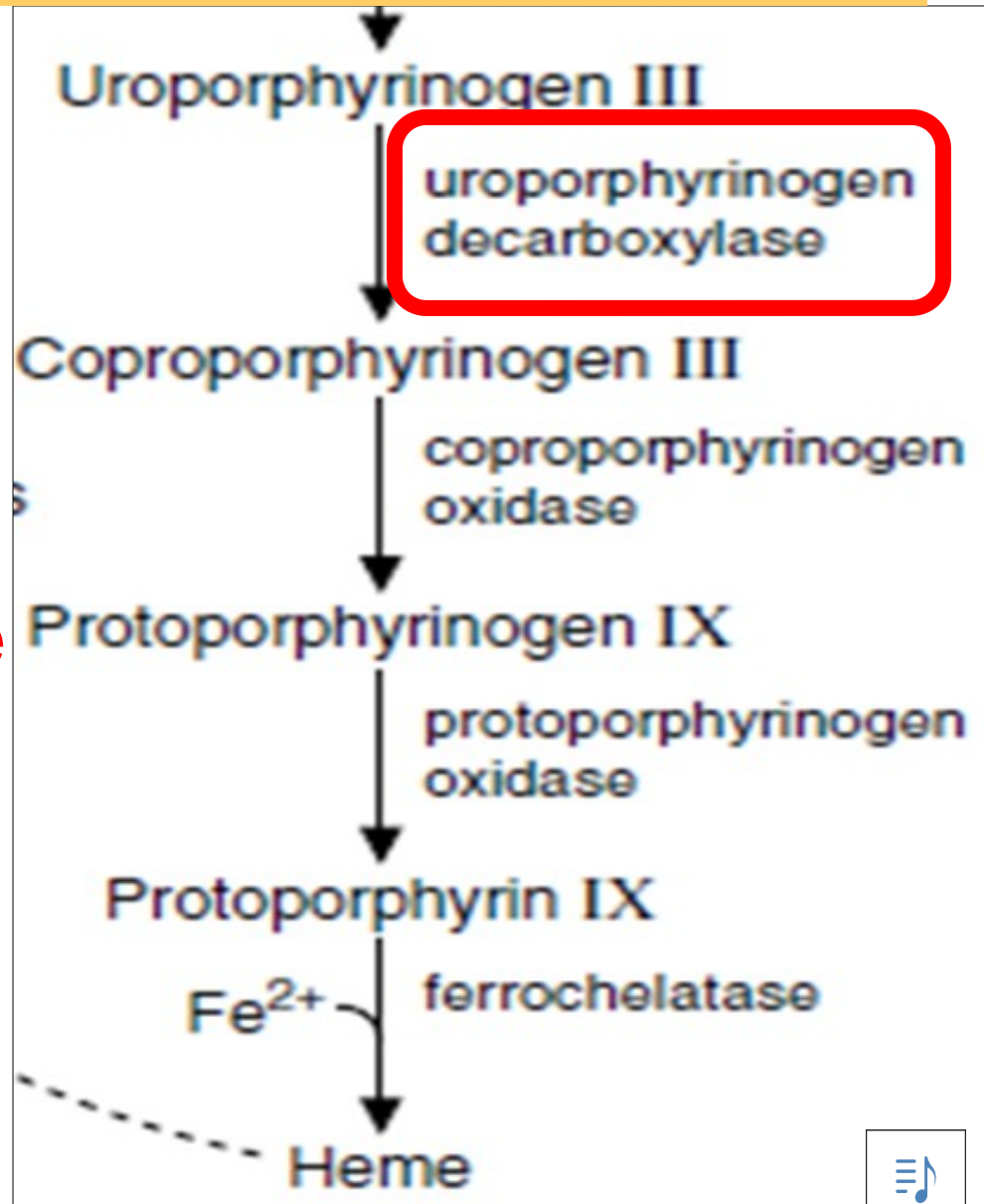
Condensation of **four** porphobilinogens produces a **linear tetrapyrrole**, which is **cyclized** forming **uroporphyrinogen III** by **uroporphyrinogen III Synthase** enzyme



4- Formation of Heme:

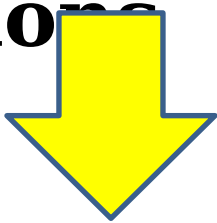
Uroporphyrinogen III undergoes decarboxylation forming coproporphyrinogen III

This reaction occurs in the cytosol

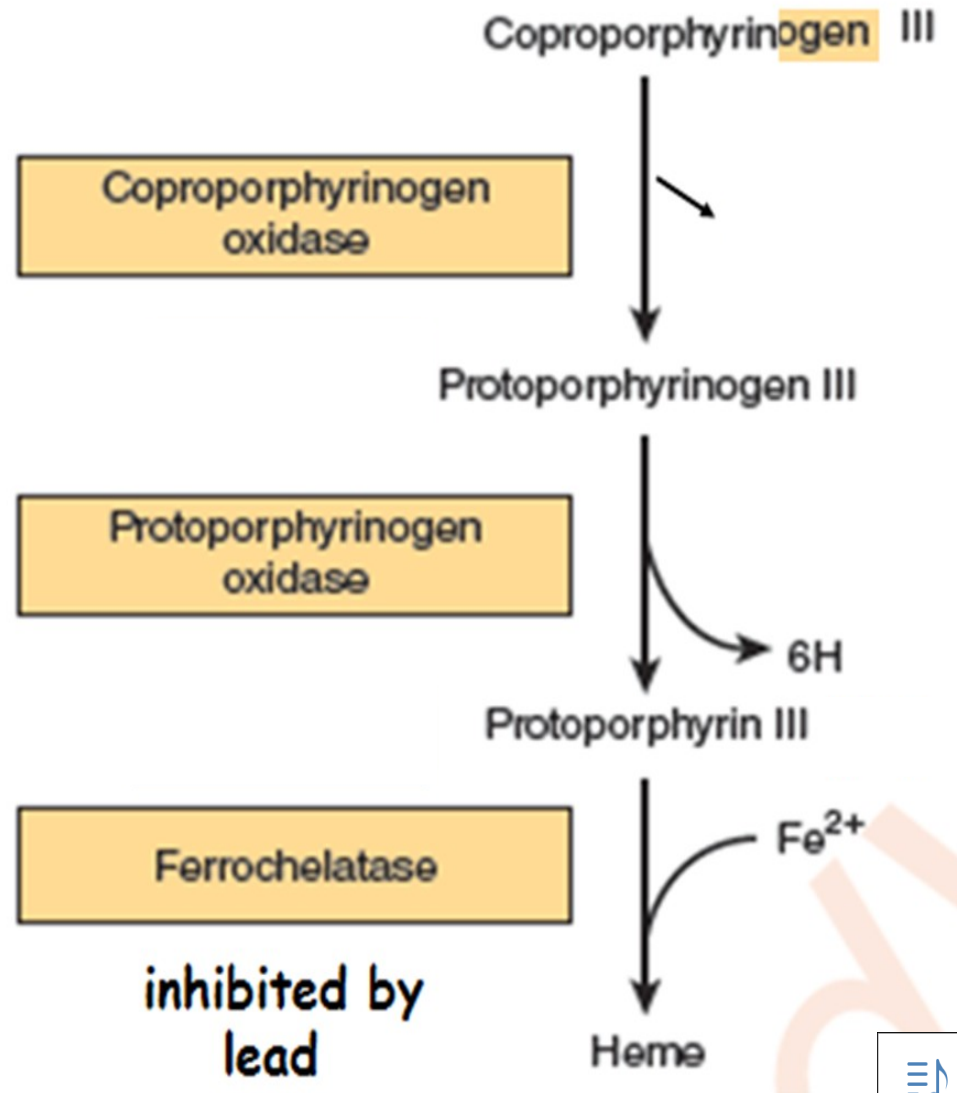


4- Formation of Heme:

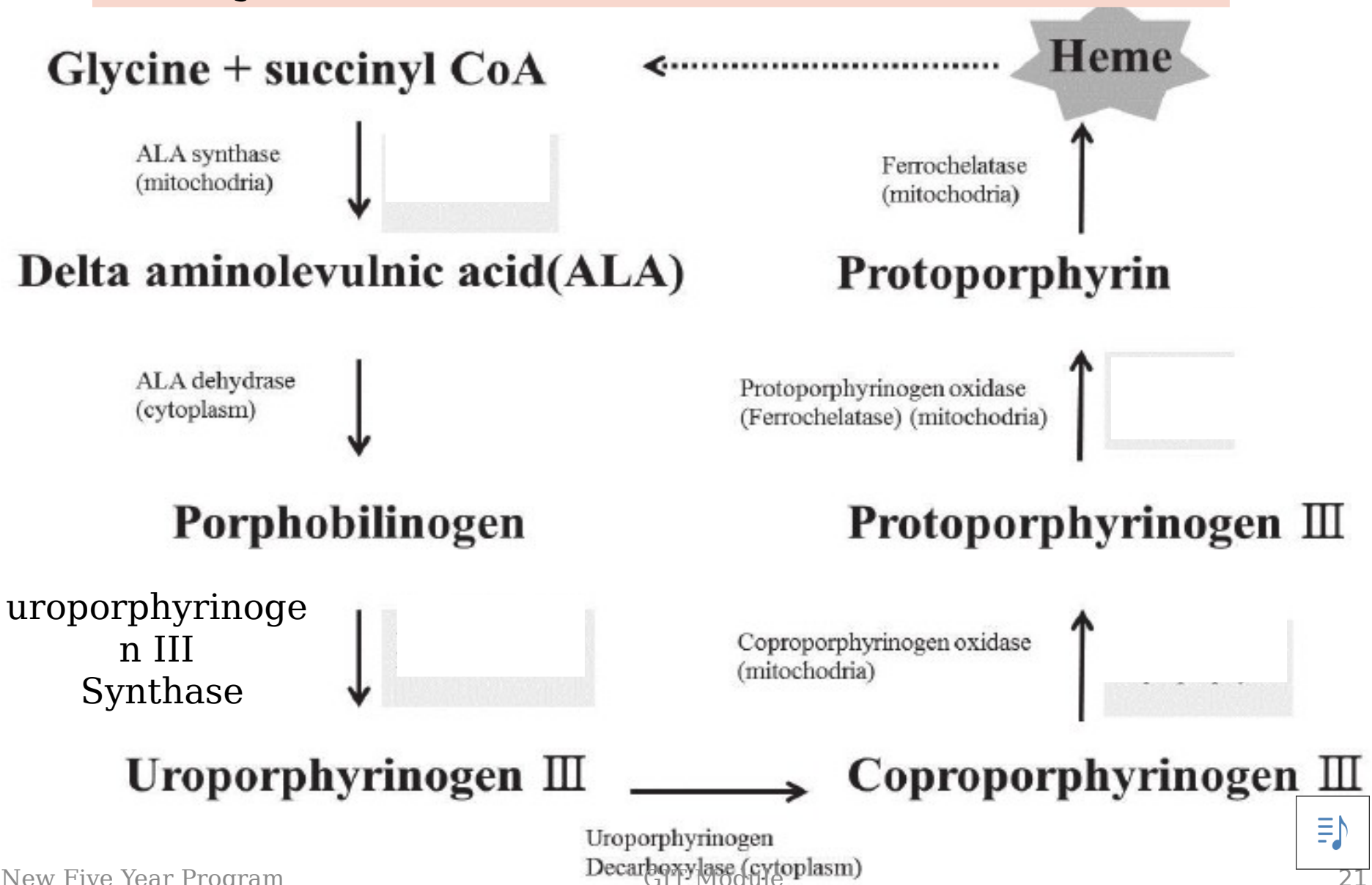
Coproporphyrinogen III enters the mitochondrion, followed by oxidation reactions.



Iron (as Fe^{2+}) is introduced into protoporphyrin by ferrochelatase enzyme.



Overall reactions of heme biosynthesis



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**An amino acid required for -2
:porphyrin synthesis is**

A. proline

B. serine

☒ C. glycine

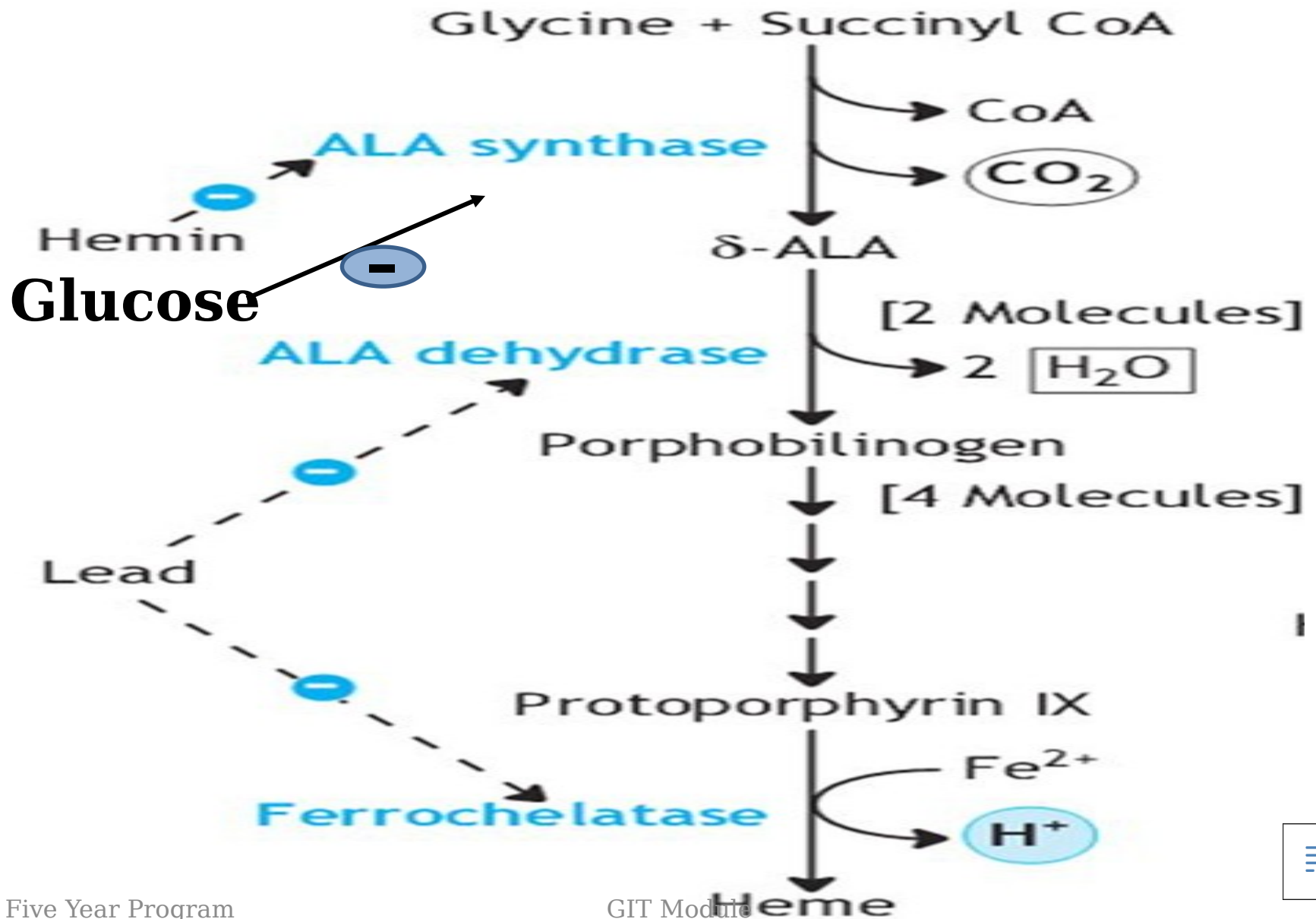
D. histidine

E. alanine

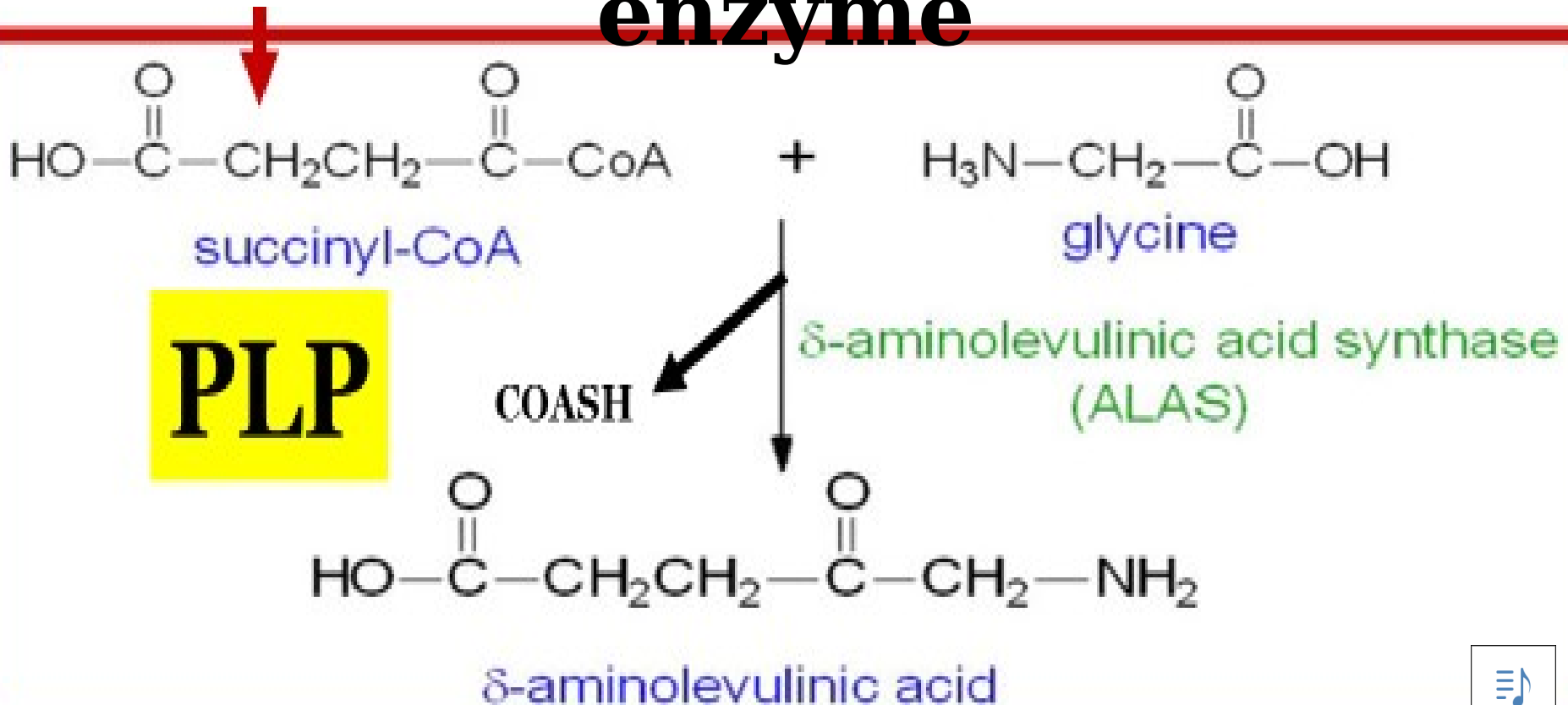


Regulation of heme synthesis

Regulation of Heme Synthesis



ALA synthase is the rate limiting regulatory enzyme



:Effect of heme (hemin) -1

When porphyrin production exceeds the availability of ,the apoproteins that require it heme accumulates and is converted to hemin by the .+oxidation of Fe²⁺ to Fe³

Hemin decreases the amount and the .activity of ALAS enzyme



Glycine + Succinyl CoA

ALA Synthase



δ aminolevulonic acid (ALA)



HEME



ALA Synthase
catalyzes first step of
heme biosynthesis
Heme end product of
the pathway act as
allosteric inhibitor

Feed Back inhibition



Effect of drugs (in liver -2 :only)

Drugs metabolized by cytochrome P450 monooxygenase in the liver .

Barbiturates
, alcohol and
carcinogens

Synthesis of cytochrome P450

Consumption of heme
a component of cytochrome P450 proteins.

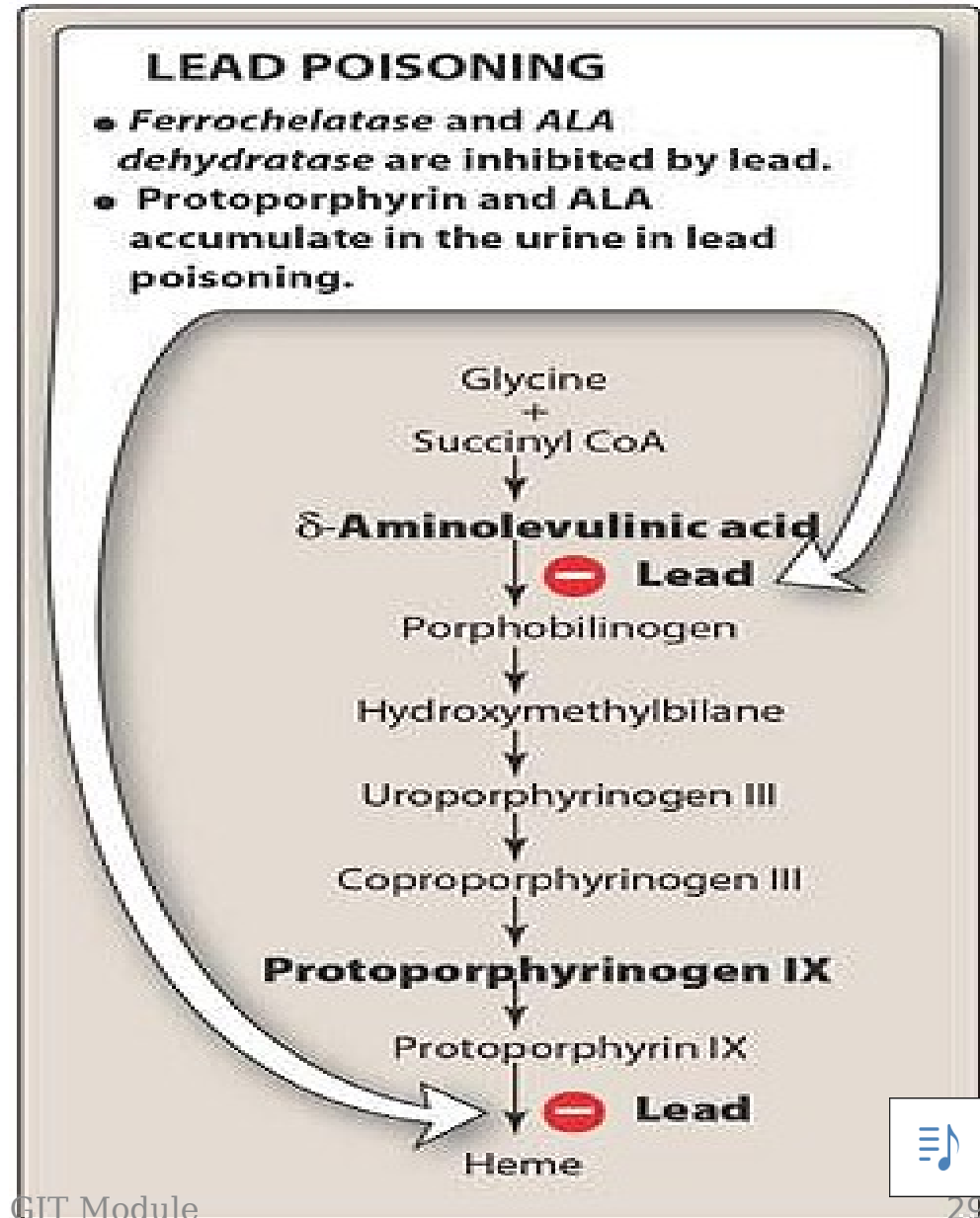
The concentration of heme in liver
Cells.

The synthesis of ALAS1 (derepression)



:Effect of Lead -3

Lead has an
inhibitory
effect on
ALA
dehydratase
&
Ferrochelatase
e



:Effect of Glucose -4

**Glucose has *inhibitory* effect
on ALA synthase**



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: δ -Aminolevulinic acid synthase activity -3

A. Is frequently decreased in liver in individuals treated with drugs, such as the barbiturate phenobarbital.

☒ B. Catalyzes a rate-limiting reaction in porphyrin biosynthesis.

C. Requires the coenzyme biotin.

D. Is strongly inhibited by heavy metal ions such as lead.

E. Occurs in the cytosol.



Summary

Heme = Iron in the ferrous state + porphyrin

- The initial reaction and the last three steps in the formation of porphyrins occur in mitochondria, but the intermediate steps occur in the cytosol
- ALA synthase is the rate limiting regulatory enzyme

Thank
you



Marwa Al

